PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 20959	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/33978	International filing date *(day/month/year)* 24 October 2003 (24.10.2003)	Priority date *(day/month/year)* 30 October 2002 (30.10.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): B01D 15/00, 15/08; C07K 14/00 and US Cl.: 210/656, 660; 530/300, 350, 359, 412, 415, 417		
Applicant MERCK & CO., INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 May 2004 (25.05.2004)	27 August 2004 (27.08.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Chih-Min Kam Telephone No. (703) 308-0916

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US03/33978

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-14 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages 15-17, filed with the letter of 18 August 2004 (18.08.2004)

☒ the drawings:
pages 1-12, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 22-28

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US05/[redacted]78

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 1-21	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 2-5 and 8-21	YES
	Claims 1, 6 and 7	NO
Industrial Applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

1. Claims 1, 6 and 7 lack an inventive step under PCT Article 33(3) as being obvious over JP 11023558 (abstract).

The reference teaches the peptides are separated by normal phase liquid chromatography using organic solvent, water, acid and/or amine in the mobile phase (abstract), which is obvious to the purification method of claims 1, 6 and 7.

2. Claims 2-5 and 8-21 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of purifying a peptide or lipopeptide using a mobile phase modifier such as a substituted amine, an amino acid or amino acid ester.

3. Claims 1-21 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

This report is based on the amendment submitted on 18 August 2004, in which original claims 2-7 and 15 have been cancelled, claims 1, 8-14 and 16-28 have been amended, and all of the pending claims are renumbered to claims 1-21.

---------- NEW CITATIONS ----------

NONE

WHAT IS CLAIMED IS:

1. A method of purifying a peptide or a lipopeptide by using a mobile phase modifier in a normal phase chromatography system to improve the selectivity and/or productivity of the purification.

2. The method as recited in claim 1, wherein the mobile phase modifier is selected from a group consisting of an amine, an amino acid or an amino acid ester.

3. The method as recited in claim 2, wherein the normal phase chromatography system includes a mobile phase and a stationary phase.

4. The method as recited in claim 3, wherein the stationary phase is selected from silica gel and alumina.

5. The method as recited in claim 4, wherein the mobile phase is a solvent system comprising one or more solvents.

6. The method as recited in claim 5, wherein the mobile phase modifier is an amine.

7. The method as recited in Claim 6, wherein the amine is selected from the group consisting of: methylamine, ethylamine, diisopropylamine, diethylamine, dimethylamine, ethylmethylamine, triethylamine, propylamine, aniline and dimethylaniline.

8. The method as recited in claim 5, wherein the mobile phase modifier is an amino acid or amino acid ester.

9. The method as recited in Claim 8, wherein the amino acid or amino acid ester mobile phase modifier is selected from the group consisting of: L-amino acids, D-amino acids, L-amino acid esters and D-amino acid esters.

10. The method as recited in Claim 9, wherein the amino acid or amino acid ester mobile phase modifier is selected from: L-proline, D-proline, *trans*-4-hydroxy-L-proline,

trans-4-hydroxy-D-proline, glycine, L-threonine, D-threonine, L-lysine, D-lysine, L-methionine, D-methionine, D-valine, L-valine and esters of the aforementioned L-and D-amino acids.

11. The method as recited in claim 10, wherein the amino acid is selected from: L-proline and D-proline.

12. The method as recited in claim 5, wherein the normal phase chromatography system is for the purification of a peptide.

13. The method as recited in claim 5, wherein the normal phase chromatography system is for the purification of a lipopeptide.

14. The method as recited in claim 13, wherein the lipopeptide is a fermentation product precursor of caspofungin, micafungin, cilofungin, andulifungin and daptomycin.

15. The method as recited in claim 14, wherein the lipopeptide is a pneumocandin B_0.

16. The method as recited in claim 15, wherein the mobile phase modifier is an amine.

17. The method as recited in Claim 16, wherein the amine mobile phase modifier is selected from the group consisting of: methylamine, ethylamine, diisopropylamine, diethylamine, dimethylamine, ethylmethylamine, triethylamine, propylamine, aniline and dimethylaniline.

18. The method as recited in claim 15, wherein the mobile phase modifier is an amino acid or amino acid ester.

19. The method as recited in Claim 18, wherein the amino acid or amino acid ester mobile phase modifier is selected from the group consisting of: L-amino acids, D-amino acids, L-amino acid esters and D-amino acid esters.

20. The method as in claim 19, wherein the stationary phase is silica gel.

21. The method as recited in Claim 20, wherein the amino acid or amino acid ester mobile phase modifier is selected from: L-proline, D-proline, *trans*-4-hydroxy-L-proline, *trans*-4-hydroxy-D-proline, glycine, L-threonine, D-threonine, L-lysine, D-lysine, L-methionine, D-methionine, D-valine, L-valine and esters of the aforementioned L-and D-amino acids.

22. The method as recited in claim 21, wherein the mobile phase is a solvent system comprising water, methanol, and ethyl acetate.

23. The method as recited in claim 22, wherein the amino acid mobile phase modifier is selected from: L-proline and D-proline.

24. The method as recited in claim 12, wherein the peptide is oxytocin or bradykinin.

25. The method as recited in claim 24, wherein the mobile phase modifier is an amine.

26. The method as recited in claim 24, wherein the mobile phase modifier is an amino acid or amino acid ester.

27. The method as in claim 26, wherein the stationary phase is silica gel.

28. A method of purifying a peptide or a lipopeptide by using a mobile phase modifier in a normal phase chromatography system to improve the selectivity and/or productivity of the purification, except that when the lipopeptide is Pneumocandin B_0, then the mobile phase modifier is not L-proline.